Highlights of ICML 2015

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Statistics, ICML 2015: a global meeting

Almost 3700 participants.

90 countries represented.

Attendees:
  • USA 465
  • Asia 392
ICML-13 Key themes

“Wealth of riches” for lymphoma treatment options

- Refinement of novel therapies
- Novel-Novel combinations
- Toxicity and late effects
- Genesis of future randomized studies

Practice-changing research
Follicular lymphoma
Follicular lymphoma in 2015: Closed Workshop Report

Increased understanding of biology, including transformation.

Focus on common progenitor cell.

Complex role of microenvironment.
OS of Patients With FL Who Relapsed Within 2 Years of R-CHOP ("Early POD"); NLCS cohort

Five-year OS (95% CI) was 50% (40.3–58.8).

80% of patients:
Outstanding OS

20% of patients:
Median OS 5 years

Casulo et al, in press JCO
Follicular lymphoma 2015: Closed workshop report

- Consensus around concept that “high risk” follicular lymphoma represents key unmet clinical need.

- Identifying these patients upfront is a high priority.

- M7-FL-IPI may represent a starting place for this effort.
  - Shrinks high risk FL-IPI group to contain worst actors

M7 FL-IPI:

- High FL-IPI
- ECOG > 1
- EP300
- FOX01
- CREBBP
- CARD11
- MEF2B
- ARID1A
- EZH2
FLASH PROJECT (abstract 122)
Results: Primary Surrogacy Evaluation (CR30)

\[ \log(HR_{PFS}) = -0.093 - 0.636 \times \log(OR_{30mCR}) \]

<table>
<thead>
<tr>
<th>Trial-level Surrogacy</th>
<th>R²</th>
<th>(95% CI)</th>
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<tbody>
<tr>
<td>WLS</td>
<td>0.88</td>
<td>(0.77, 0.96)</td>
</tr>
<tr>
<td>Copula</td>
<td>0.86</td>
<td>(0.72, 1.00)</td>
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**Individual-level GOR (95% CI)**

| 11.84 (10.03, 13.65) |  |

30-month complete response rate met the prespecified surrogacy qualification criteria for PFS
Conclusions: FLASH project

Principal candidate CR30 met the surrogacy qualification criteria for PFS overall and within trial types.

Correlation of treatment effects on PFS and CR30 was more marked in patients with advanced disease or high FLIPI score.

CR30 may be considered an appropriate primary endpoint in future first-line FL studies.
Hodgkin lymphoma
**RATHL Trial**

**Stage 2u, 3, 4 HL**

1. **PET 1 (Staging)**
   - 2 cycles ABVD
     - Full dose, on schedule

2. **PET 2**
   - **PET 2 +ve**
     - 4 cycles BEACOPP-14
       - or 3 eBEACOPP
     - **PET 3**
       - **PET 3 +ve**
         - RT or salvage regimen
       - **PET 3 -ve**
         - 2 cycles BEACOPP-14 or 1 eBEACOPP
         - No RT

   - **PET 2 -ve**
     - Randomise
     - 4 cycles ABVD
     - 4 cycles AVD

     - Follow-up (no RT)
RATHL Trial: Preliminary results (Abstract 8)

Overall results:
• 3 year PFS 82.5%; 3 year OS 95%

84% of patients had negative PET scan after two cycles of ABVD.

ABVD 3 year PFS 85%
AVD 3 year PFS 84%

Only 14 deaths on each arm

16% of patients had positive PET scan after ABVD.

3 year PFS 70%
RATHL Trial: Preliminary results (Abstract 8)

My thoughts:

1. Safety of eliminating bleomycin for PET negative patients after two cycles of ABVD.

2. Escalation to BEACOPPesc for PET positive patients appears to have favorable outcome, confirming S0816 experience.

3. PET scans are not the “total” answer in HL. 15% of patients who are PET negative after two cycles of ABVD still have subsequent PFS events, again confirming S0816 experience.
H10 trial: PET2 positive design

H10F

- 2 ABVD
- R

H10U

- 2 ABVD
- R

- 2 ABVD
+ 2 BEACOPPesc+IN-RT 30(+6)

Hodgkin - CS I/II – supradiaphragmatic - untreated - 15-70 yrs - no NLPHL
PET+ group: BEACOPPesc vs. ABVD progression-free survival (PFS)

**HR (95% CI) = 0.42 (0.23, 0.74); p=0.002 *  
5-yr PFS: 91% vs. 77%**
H10 trial

OS improvement 5yr 89% (ABVD) to 96 (BEACOPPε)%.

Suggests safety and efficacy of therapy escalation in PET positive patients.

Long-term toxicity of combined BEACOPPesc and XRT need to be watched carefully given OS favorability in ABVD arm.
LP cells of NLPHL show functional B cell receptors and ongoing somatic hypermutation.
Involvement of Moraxella catarrhalis in pathogenesis of NLPHL (abstract 94)

Chronic antigen stimulation

Aim of study was to identify target antigens of BCRs of LP cells.

Several IgD positive cases reacted to M catarrhalis

Suggests NLPHL derives from clonal evolution of polyclonal B-cell response against M catarrhalis
Diffuse large B-cell lymphoma
IELSG32 trial (abstract 9): Thiotepa and rituximab in primary CNS lymphoma

- CR; 2 yr OS:

  MTX-AraC: 23%; 40%

  MTX-AraC-R: 30%; 58%

  MTX-AraC-R-TT: 49%; 66%

Subsequent randomization:
- XRT vs. ASCT
Overall Survival: Primary CNS NHL

122 (56%) pts are alive
  A: 29 (39%)
  B: 41 (59%)
  C: 52 (69%)

LTF: 6 pts (2-17 months)

Causes of death (n= 97):
- lymphoma 73
- toxicity (1° line) 15
- toxicity (salvage) 2
- neurotoxicity (rel-free) 2
- others while rel-free 4
- unknown 1

A vs. B= 0,01
A vs. C= 0,0005
B vs. C= 0,24
IELSG32 trial (abstract 9): Thiotepa and rituximab in primary CNS lymphoma

High risk group of patients.

Outcomes inferior to previous experiences.

How does this compare with other induction regimens?
CAR-T cell therapy for relapsed/refractory DLBCL (Abstract 139)

19 patients with DLBCL; 31% prior ASCT

7 patients not evaluable for response (inadequate collection; early progression, etc.)

5/12 patients with DLBCL had a CR; 1 additional PR.

CNS and cytokine release toxicity

6 month PFS only 37%
CAR Modified T Cells Against CD19 in R/R Diffuse Large B Cell Lymphoma

DLBCL: PFS (days)

Ongoing clinical responses
Days to progressive disease
CAR Modified T Cells Against CD19 in R / R Follicular Lymphoma

Ongoing clinical responses

Days to progressive disease

FL: PFS (days)

13413-04
13413-07
13413-11
13413-13
13413-15
13413-19
13413-24

FL: Progression-free Survival

N = 7
Median not reached
Median follow-up 290 days

Days

0.00
0.25
0.50
0.75
1.00

Ongoing clinical responses

Days to progressive disease
Thoughts on CAR-T for NHL

Subset of patients appear to have prolonged responses.

In aggressive lymphoma, results have been less favorable than in B-ALL.

Exportability?

In MRD states, like after ASCT?

Ongoing studies at many institutions.
Double hit DLBCL: in vitro and in vivo (146)

(KPT-330)

- Selective inhibitor of nuclear export (XPO1)
- Forces retention of tumor suppressor proteins and reduces proto-oncogene

Single agent activity observed in limited number of double hit DLBCL patients on clinical trial.

? Combination strategies
Prognostic indices
# The CLL-IPI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adverse factor</th>
<th>Grading</th>
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<tbody>
<tr>
<td>TP53 (17p)</td>
<td>deleted and/or mutated</td>
<td>4</td>
</tr>
<tr>
<td>IGHV status</td>
<td>unmutated</td>
<td>2</td>
</tr>
<tr>
<td>B2M, mg/L</td>
<td>&gt; 3.5</td>
<td>2</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>Binet B/C or Rai I-IV</td>
<td>1</td>
</tr>
<tr>
<td>Age</td>
<td>&gt; 65 years</td>
<td>1</td>
</tr>
</tbody>
</table>

| Prognostic Score | 0 - 10 |

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Score</th>
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<tbody>
<tr>
<td>Low</td>
<td>0 – 1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2 – 3</td>
</tr>
<tr>
<td>High</td>
<td>4 – 6</td>
</tr>
<tr>
<td>Very High</td>
<td>7 – 10</td>
</tr>
</tbody>
</table>
Risk groups of CLL-IPI

Training dataset [N = 1192]

$C$-statistics = 0.724 [95% CI, 0.689 – 0.758]

Internal validation dataset [N = 575]

$C$-statistics = 0.777 [95% CI, 0.732 – 0.820]
IPI for patients with CLL (abstract 54)

N=3472 from 8 phase 3 trials

5 independent predictors for OS were identified:
  - age (>65 yr)
  - clinical stage (>Rai0)
  - del(17p) and/or TP53 mutation
  - IGHV mutation status (MS)
  - serum $\beta_2$-microglobulin [>3.5 mg/L]

Will this hold up in ibrutinib/idelalisib era?
Mantle cell lymphoma: Prognostic value of proliferation, cytology and growth pattern (58)

N=709 MCL consortium patients.

MIPI + Ki-67 index (30% cut-off)

PFS (5-year rates, 67%, 46%, 29% and 16%, \( p < 0.0001 \))

OS (5-year rates, 85%, 72%, 43% and 17%, \( p < 0.0001 \))

Suspect OS will be very different in ibrutinib/lenalidomide era
WHO lymphoma classification update (abstract 4)

Expect publication in August 2016.

Ongoing process; not yet complete.

DLBCL:

1. Distinguish GCB/nonGCB in all cases, using either IHC, or possibly Lymph2Cx.

2. Include all double and triple hit lymphoma in a single new category: “high grade B-cell NHL with bcl-2/bcl-6/and myc.”

3. Double expressor lymphomas will not be separated.
Take-home messages from ICML-13: Changes in my practice after the meeting

1. Low threshold to eliminate bleomycin for PET negative advanced stage HL after ABVD x 2.

2. Consider MATRIX regimen as a standard for primary CNS lymphoma.

3. Escalating to BEACOPP in both early and advanced stage HL in patients PET positive after ABVD x 2.

4. Ensure your pathologists are ready for WHO changes to DLBCL in 2016:
   - Routine cell of origin determination
   - Routine FISH of myc and bcl-2
Acknowledging our Lugano hosts!
Thank you